Effect of Music Intervention during Weaning Trials in a Long Term Acute Care Hospital – A 6 Day Prospective Randomized Crossover Trial

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Abstract

Objective: To examine the effect of patient-selected music intervention during daily weaning trials for patients on prolonged mechanical ventilation.

Design: Randomized crossover repeated measures design.

Setting: Long-term acute care hospital.

Patients: Patients on mechanical ventilation for ≥ 4 days undergoing daily weaning trials.

Intervention: Patients were randomized to patient-selected music vs no music on the first day of the intervention; provision of music was alternated for 6 days, resulting in 3 music and 3 no music days for each patient. During weaning trials on music days, data were obtained for 30 minutes prior to music listening and continued for 60 minutes while patients listened to selected music (total 90 minutes). On no music days, data were collected for 90 minutes.

Measurements and Main Results: Outcome measures included heart rate (HR), respiratory rate (RR), arterial oxygenation (SpO_2), blood pressure (BP), dyspnea and anxiety assessed with a visual analog scale (VAS-D, VAS-A) and daily weaning duration (hours). Of 31 patients enrolled, 23 completed the 6-day intervention. Patients were 61.6 ± 10.9 years of age, 74% male, and 96% white. A multivariate mixed-effects model analysis demonstrated significant decreases in HR, RR, VAS-A, and VAS-D and a significant increase in daily weaning duration on music days ($p<0.05$).

Conclusion: Providing patient selected music is a simple, potentially beneficial intervention for LTACH patients during daily weaning trials. Further study is indicated to test ability of this intervention to promote weaning success in LTACH patients and benefits earlier in the weaning process.

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PREFACE

The study was supported by two grants: Leslie A. Hoffman Endowed Acute Care Research Funding and Pauline Thompson Clinical Nursing Research Award. The principal investigator would like to acknowledge the individual contributions of her dissertation chair, co-chair, committee members and Michael Donahoe, MD for his support of the study. She would also like to thank her parents, brother, friends and classmates for their support.

1.0 INTRODUCTION

Prolonged mechanical ventilation is a major concern to patients, caregivers, and clinicians (Carson et al., 2012; Hermans et al., 2014; Herridge et al., 2011; Leroy, Devos, Lambiotte, Thevenin, & Leroy, 2014). By 2020, the number of patients who require prolonged mechanical ventilation is projected to reach 600,000 cases in the United States and account for nearly two-thirds of the cost for all resources devoted to mechanical ventilation (Zilberberg, de Wit, & Shorr, 2012; Zilberberg, Luippold, Sulsky, & Shorr, 2008). Among strategies tested to achieve liberation from mechanical ventilation, weaning protocols and approaches incorporated in the ABCDE (awakening, breathing, delirium management, early exercise/mobility) bundle have been shown to improve patient outcomes, including weaning success, in the intensive care setting (Balas et al., 2013; Blackwood et al., 2011; Nichols & O'Rourke, 1988). When these strategies are not successful, patients may be transferred to a rehabilitation focused setting, such as a long-term acute care hospital, to complete the weaning process.

Long-term acute care hospitals (LTACH) provide complex inpatient care for patients in the recovery phase of illness and are among the fastest growing and highest paid providers of post-acute care in the United States (Kahn et al., 2013; Kim et al., 2015). A number of studies have examined outcomes of mechanically ventilated patients admitted to a LTACH, but the majority are descriptive (Dermot Frengley, Sansone, Shakya, & Kaner, 2014; Kahn, Benson,

Appleby, Carson, & Iwashyna, 2010; Scheinhorn et al., 2007; Seneff et al., 2000). Although many studies have tested interventions to promote weaning in the intensive care setting, evidence regarding best strategies in a LTACH setting is limited to one study (Jubran et al., 2013).

Patients who require prolonged mechanical ventilation are at high risk of psychological morbidity (Bradt et al., 2015; Kim et al., 2015; Nelson et al., 2004). From a study of 50 patients who were transferred to a respiratory care unit for weaning from prolonged mechanical ventilation, Nelson and colleagues (2004) found that over 60% reported dyspnea during weaning. More than 60% also reported psychological symptoms "frequently" or "almost constantly." In this situation, weaning trials may exacerbate symptoms, resulting in early termination of the trial and prolong need for support. We therefore reasoned that a strategy targeted at reducing stress during weaning might be especially beneficial in this setting.

Music is a non-pharmacologic intervention that can be used as a complementary adjunct in the care of patients supported by mechanical ventilation (Chan, Chung, Chung, & Lee, 2009). Music is a distracting agent that refocuses attention and influences emotions. Music may also promote relaxation via biologic mechanisms that include a reduction in blood cortisol (Beaulieu-Boire et al., 2013; Tracy & Chlan, 2011). Prior studies report that music intervention can relieve pain and anxiety and increase comfort in patients admitted to an intensive care unit (Bradt & Dileo, 2014; Chan et al., 2009; L. L. Chlan et al., 2013; Han et al., 2010; Hunter et al., 2010; Korhan, Khorshid, & Uyar, 2011). A recent Cochrane review concluded that listening to music consistently reduced respiratory rate, systolic blood pressure, and had an anxiety-reducing effect in mechanically ventilated patients (Bradt & Dileo, 2014). In this review, which included 14 clinical trials (805 patients on mechanical ventilation), music listening resulted in a reduction in

anxiety that, on average, was 1.11 standard deviation units greater (95% CI -1.75 to -0.47, p = 0.0006) than usual care.

We were able to identify only one study that tested music intervention as a means to promote weaning from mechanical ventilation (Hunter et al., 2010). In this study, 51 patients listened to music for 40-60 minutes during weaning trials three times a week. Findings showed a significant reduction in respiratory rate, heart rate and increased patient satisfaction ($p<0.05$), but the comparison was to a retrospective sample. No studies were identified that tested effects of music intervention to promote weaning in a LTACH. Purpose

1.1 SPECIFIC AIMS

The specific aims of the proposed research project were to explore: 1) changes in physiological parameters (HR, RR, arterial oxygen saturation [SpO_2], blood pressure [BP]); 2) changes in patient's anxiety and dyspnea; and 3) the duration of weaning trials (hours) before and after a music intervention using a prospective crossover design method.

2.0 BACKGROUND AND REVIEW OF LITERATURE

2.1 PROLONGED MECHANICAL VENTILATION IS COMMON AND COSTLY WITH A POOR PROGNOSIS

Mechanical ventilation, an intervention used for patients experiencing respiratory failure, is one of the most frequently used treatment methods in the intensive care unit (ICU) (Cox et al., 2009). Mechanical ventilation is also recognized as a major critical care treatment modality that is used in settings beyond ICU. Examples of these facilities include step-down units, noninvasive respiratory care units, and LTACH (Scheinhorn et al., 2007). In each of these settings, patients who require mechanical ventilation may experience symptom distress that contributes to difficulty regaining ability to breathe without support from the ventilator (Campbell & Happ, 2010; Rotondi et al., 2002; J. A. Tate, Devito Dabbs, Hoffman, Milbrandt, & Happ, 2012).

A Consensus Conference in the year 2008 recommended that prolonged mechanical ventilation (PMV) be defined as the need for continual assistance from a mechanical ventilator for at least 6 hours per day for at least 21 days (White, O'Connor, & Kirby, 2008). This definition has been challenged as too lengthy. Reports indicate that as many as 33% of all ICU patients require PMV if defined as requiring this support for 4 days or longer (Cox et al., 2009). This designation conforms to the definition of the two diagnosis related group (DRG) codes (541 and 542) that are used by Medicare to designate long term mechanical ventilation and

tracheostomy. For this reason, it facilitates retrieval of data from electronic repositories which can be linked to other variables of interest (Cox et al., 2007). Consequently, a time period of 4 days or longer has become the more common definition of PMV.

PMV is a major concern to patients, caregivers, and clinicians due to the increasing number of patients who require this support and associated costs. By 2020, the number of patients who require PMV is projected to reach 600,000 cases, compared to 250,000 cases in 2000, with associated hospital costs of $50-60 billion (Zilberberg, de Wit, Pirone, & Shorr, 2008). Zilberberg, et al. (2008) using data (763,501 mechanically ventilated patients) from the National In-Patient Survey reported that median hospital costs for these patients were $13,434 (interquartile range from $7,420 to $24,194) and for PMV $40,903 (interquartile range $24,905 to $68,865). Although PMV subjects comprised only 39% of all persons undergoing mechanical ventilation, they accounted for 64% of all annual in-patient costs. In this study, PMV was defined as >96 hours on mechanical ventilation.

In addition to the disproportionate utilization of health care resources and its high cost, PMV patients experience a poor prognosis (Baldwin et al., 2013; Carson et al., 2012; Cox et al., 2007; Cox et al., 2009; Nelson et al., 2004; Scheinhorn et al., 2007). In 2001, the National Association of Long Term Hospitals (NALTH) commissioned a multicenter study to investigate outcomes of care in the post-ICU weaning population. They reported that a substantial minority of patients admitted to these facilities (25%) died during their hospital stay and approximately 33% were alive 12 months after admission to a LTACH (Scheinhorn et al., 2007). Carson and colleagues (2012) reported that of 260 PMV patients recruited, 1 year mortality was 48%. More recently, Baldwin and colleagues (2013) reported that 6 month mortality for elderly patients were

admitted to an ICU was 30%. Given these outcomes, strategies to improve the quality of life and reduce healthcare costs for this patient population are essential.

2.2 MECHANICAL VENTILATION IS ASSOCIATED WITH DISTRESSING SYMPTOMS

Mechanical ventilation creates a distressing physiological and psychological experience for patients. During mechanical ventilation, the combination of oral intubation, heavy sedation, and physical restraint renders patients unable to experience the presence of their family members, communicate about pain, uncomfortable symptoms and treatment preferences or move freely (Happ et al., 2011; Nelson et al., 2001; Puntillo, Smith, Arai, & Stotts, 2008; Rotondi et al., 2002). Zilbergerg and colleagues (2008) reported that PMV patients report a diminished quality of life, functional and cognitive limitations and require prolonged informal care-giving assistance. Jubran and colleagues (2010) found that 42% of 336 patients had depressive disorders. Patients with depressive disorders were more likely to experience weaning failure than those without (61% vs 33%, p=.0001). We therefore reasoned that an intervention targeted at reducing anxiety and dyspnea might benefit mechanical ventilated patient during their weaning trials.

Anxiety is highly prevalent for mechanical ventilated patients (L. Chlan & Halm, 2013; J. A. Tate et al., 2012). From a series of studies aiming to improve mechanical ventilated patients' communication in the ICU setting, Happ and colleagues reported that patients experienced many challenges attempting to communicate with clinicians and family members, a source of stress

and anxiety (Happ et al., 2010; Happ et al., 2011; Nilsen, Sereika, & Happ, 2013; J. A. Tate et al., 2012; J. A. Tate et al., 2013). Wong and colleagues (2001) reported that anxiety was present in 70% to 80% of intensive care patients, especially in ventilator-dependent patients whose respiratory function failed to maintain adequate gas exchange and systemic oxygen generation. In descriptive studies, the majority (85%) of mechanically ventilated patients (N=106) reported some anxiety (McKinley, Stein-Parbury, Chehelnabi, & Lovas, 2004) and over half (60%) reported that they felt "scared" some to most of the time (Rattray, Johnston, & Wildsmith, 2004).

Anxiety is a state marked by apprehension, increased motor tension, and autonomic arousal and, as noted in the previously cited studies, is a common occurrence for patients undergoing mechanical ventilation (McCartney & Boland, 1994). Stress and anxiety can increase sympathetic nervous system stimulation with a consequent increase in HR, RR, and BP that, in turn, results in physiological difficulties and psychological distress (L. L. Chlan, 2010). This outcome can play a major role in preventing patients from regaining the ability to breathe independently from the ventilator and prolong need for ventilator support (Thomas, 2003; Wong et al., 2001). Although physiologically stable, ventilator-dependent patients may still fail the weaning process because of psychological distress. Studies show that approximately 10-25% of patients who require mechanical ventilation have difficulty weaning prior to ICU discharge (White et al., 2008).

2.3 CURRENT STRATEGIES FOR MANAGING STRESS AND ANXIETY AMONG PATIENTS ON MECHANICAL VENTILATION

The standard treatment for reducing stress and anxiety among critically ill patients involves intravenous administration of sedatives and analgesics (Jackson, Proudfoot, Cann, & Walsh, 2010). Patients receiving mechanical ventilation often receive heavy sedation and may be physically restrained in response to the discomfort and distress of intubation (Hofso & Coyer, 2007a, 2007b). Medications most frequently administered include opioids, benzodiazepines, anesthetics, and neuroleptics, either by intermittent intravenous bolus or continuous infusion (Barr & Pandharipande, 2013; Egerod, Christensen, & Johansen, 2006). However, the drugs used to control the distress are expensive, both directly and indirectly (Lee, Chung, Chan, & Chan, 2005). These medications have many side effects including nausea and vomiting, respiratory depression, urinary retention, hypotension, venous stasis, respiratory and extremity muscle weakness or atrophy (A. Arroliga et al., 2005; L. L. Chlan, 1998). In addition, sedatives may prolong the weaning process (Sessler & Varney, 2008). Studies have demonstrated that the use of continuous sedation is associated with the prolongation of mechanical ventilation, which in turn leads to high hospital costs (A. Arroliga et al., 2005; A. C. Arroliga et al., 2008; Kollef et al., 1998; Seneff, Wagner, Thompson, Honeycutt, & Silver, 2000). Protocolized sedation or daily sedation interruption has been successfully used to minimize the use of sedatives and reduce the duration of mechanical ventilation and hospital length of stay (Kress, Pohlman, O'Connor, & Hall, 2000; Mehta et al., 2012). However, challenges exist with these interventions (Guttormson, Chlan, Weinert, & Savik, 2010; Sneyers et al., 2013; Tanios, de Wit, Epstein, & Devlin, 2009). Examples of challenges include achieving consensus about the protocol to be used and insuring

that it is consistently applied (Sneyers et al., 2013). Guttormson, et al. (2010) reported that protocol adherence was positively related to nurses' attitude towards the efficacy of sedation for mechanical ventilated patients ($p<0.01$).

Other non-pharmacologic approaches may also be used. Meade et al. (2001) reviewed eight randomized controlled studies that investigated a variety of non-pharmacological interventions to assist with the weaning process. These interventions ranged from enteral nutrition, to exogenous growth hormone, and biofeedback. Thomas (2003) discussed the effective use of hypnosis and relaxation, patient education and information sharing, music therapy, and supportive touch with patients on mechanical ventilation to reduce common stressors of ventilation, noting that few published studies explored non-pharmacological interventions to alleviate patient perceived stressors and anxiety. Tracy and Chlan (2011) suggested that an effective non-pharmacological approach to manage ventilator associated stressors and anxiety could be the use of a music intervention.

2.4 MECHANISM OF MUSIC THERAPY AND METHODS OF IMPLEMENTATION

Music therapy has a long history of healing and curing effects. As defined by Munro and Mount (1978), "music therapy is the controlled use of music and its influence on the human being to aid in physiologic, psychological, and emotional integration of the individual during treatment of an illness or disability". Music uses the technique of distraction in order to influence a person's emotional feeling and physiological responses. Altshuler cited in Davis' article (2003) explains

how music can change moods consciously at the cortical level through stimulation of imagination and intellect. Music might stimulate an automatic response at the thalamic level where emotions and feelings are transmitted to the cerebral hemisphere in order to affect the moods both consciously and unconsciously (Wong et al., 2001). Brody cited in Wong's article (2001) suggests that music can affect the brain network through the limbic system by stimulating the pituitary gland to release endorphins with the pleasure of listening to music. Beaulieu-Boire and colleagues (2013) tested two 1-hour daily periods of music-vs-sham-MP3 listening in 49 sedated mechanically ventilated patients. They reported a significant decrease in cortisol and prolactin blood concentrations and a significant increase in adrenocorticotrophic hormone (ACTH)/cortisol ratio during music listening compared with sham MP3 listening. These findings suggest a potential mechanistic explanation for the effect of music intervention.

Music may also promote relaxation via physiological and/ or psychological entrainment. Entrainment is a physics principle in which two objects vibrating at similar frequencies tend to cause mutual sympathetic resonance and vibrate at the same frequency (Maranto, 1993). Musical stimuli and physiological processes (HR, RR, BP, temperature, adrenal hormones) are composed of vibrations that occur in a regular, periodic manner and consist of oscillations. Musical stimuli, specifically rhythm and tempo, can be used as a synchronizer to influence changes in physiological responses through entrainment (L. L. Chlan, 2009). When using music to induce relaxation through entrainment, it should have a tempo at or below a resting HR, predictable dynamics, fluid melodic movement, pleasing harmonies, regular rhythm without sudden changes, and tonal qualities that include strings, flute, piano, or specially synthesized tones. These musical properties are used to induce relaxation by causing body rhythms to slow or entrain to the slower beat of the music. Music with slow, steady, and repetitive rhythm is thought to exert a hypnotic

effect and contribute to relaxation and anxiety reduction through cognitive quieting and altered states of consciousness (L. L. Chlan, 2009). Because physiological relaxation is incompatible with anxiety, music can alter perceived levels of anxiety while facilitating more relaxed physiological responses. Music can decrease anxiety by occupying attention channels in the brain with meaningful, distractive, soothing auditory stimuli rather than stressful environmental stimuli (L. L. Chlan, 2009).

Prior studies suggested that music preference is a major influencing factor on intervention outcomes; cultural preference and age are also major influences (Tracy & Chlan, 2011). Thus, a semi-structured approach that allows selection of songs from those identified by the researcher is advocated (Tang & Vezeau, 2010). A range of 60-80 beats per minute is most commonly used as it mimics the adult human HR (Tracy & Chlan, 2011). Session length is typically 20 to 120 minutes, with 30 minutes most commonly used in ICU settings. Outcome measures vary, but are advised to include both physiological and psychological measures (Tang & Vezeau, 2010). The goal of this study was to provide findings which are methodologically sound and therefore provide sound evidence for use (or non-use) of this intervention.

2.5 EFFECT OF A MUSIC INTERVENTION IN MECHANICALLY VENTILATED PATIENTS

Music intervention, defined as the therapeutic use of music that affects patient health and well-being, is a non-pharmacologic nursing intervention that has been shown to be effective in promoting relaxation and decreasing anxiety with critically ill patients receiving mechanical

ventilatory support. Outcomes most commonly reported are a reduction in anxiety and physical parameters (HR, RR, BP) (Almerud, 2003; L. L. Chlan, 1995, 1998; L. L. Chlan, Engeland, Anthony, & Guttormson, 2007; L. L. Chlan et al., 2013; Lee et al., 2005; Wong et al., 2001). A recent Cochrane review concluded that music listening consistently reduced respiratory rate (RR), systolic blood pressure and had an anxiety-reducing effect in mechanically ventilated patients (Bradt & Dileo, 2014). In this review, which included 14 trials (805 critically patients on mechanical ventilation), music listening resulted in a reduction in anxiety that, on average, was 1.11 standard deviation units greater (95% CI -1.75 to -0.47, P = 0.0006) than usual care.

Most of the music studies used an experimental (pre-post) design with randomization to group (music or control) to test effectiveness. Although methods varied, results were uniformly positive. In a randomized clinical trial that enrolled 373 mechanically ventilated patients from 12 ICUs, a patient directed music intervention resulted in greater reduction in anxiety, sedation frequency and sedation intensity compared to a noise control and usual care group (L. L. Chlan et al., 2013). Lee and colleagues (2005) reported a significant reduction in HR, RR, systolic and diastolic BP ($p<0.05$) when music was administered for the same interval compared to controls (no music) in 64 mechanically ventilated patients. Almerud & Peterson (2003) reported a significant reduction in systolic and diastolic BP ($p=.05$) in 10 patients who listened to classical music for 30 minutes at night compared to controls (rest alone). Studies also reported music listening decrease the need for sedative drugs (Beaulieu-Boire et al., 2013; L. L. Chlan et al., 2013; Conrad et al., 2007).

Although studies have shown the benefit of music intervention for mechanically ventilated patients, we were only able to identify one study that tested music intervention as a means to promote weaning from mechanical ventilation (Hunter et al., 2010). In this study, the

music therapy intervention consisted of 45 to 60-minute per session three times a week during weaning trials. Of 61 subjects recruited, 51 (84%) completed the study with an average of 4 sessions per subject. Reasons for attrition included: delirium, hard of hearing, overwhelmed or asked to withdraw. The intervention resulted in a significant decrease in HR (p=.0267) and RR (p=.001) and high patient/nurse satisfaction. However, the results were compared to matched historical controls admitted to the ICU within ≤ 2 yrs. Use of a historical, rather than a concurrent comparison group, is less than ideal, given rapid changes in critical care.

Given these positive findings, it is puzzling that music is not more commonly used in ICUs as a nursing intervention. It is the applicant's goal to promote greater use of this strategy through a stronger evidence base for practice.

2.6 SIGNIFICANCE AND INNOVATION

The study was significant and innovative because:

1. Results support use of a simple, low-cost nursing intervention to promote weaning from mechanical ventilation.
2. It is one the first to evaluate the ability of a music intervention to facilitate weaning from PMV using a prospective crossover design.
3. Findings provide a comprehensive evaluation of outcomes, including change in physiological (HR, RR, BP, SpO_2), anxiety and dyspnea, and daily weaning duration (hours) than in prior studies.

4. Few prior studies have examined interventional studies on patient outcomes in a LTACH setting.

If successful, this low-cost nursing intervention could be easily implemented in critical care and long term care settings in the United States and other countries or regions.

3.0 STUDY FRAMEWORK

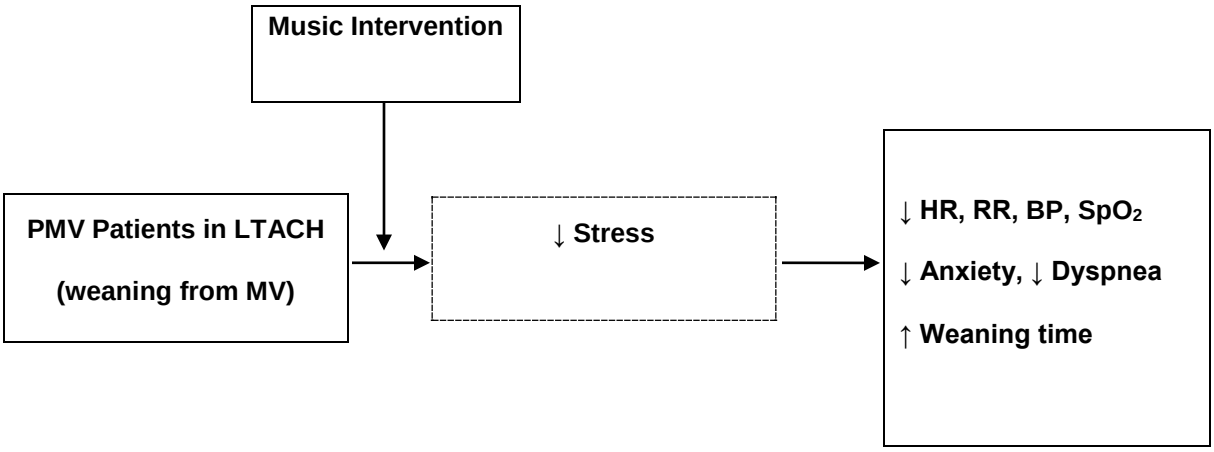

Figure 1. Study Framework

As shown in Figure 1, music intervention might reduce stress and, as a consequence, lead to a reduction in HR, RR, BP, anxiety, and dyspnea. If results are positive, music intervention should therefore increase the duration of weaning trials.

4.0 RESEARCH DESIGN AND METHODS

4.1 DESIGN

The study used a prospective crossover repeated measures design. Patients were randomized into 2 music intervention orders for 6 days during their scheduled weaning trial with use of music alternated each day: 1) order 1 = music (day 1), no music (day 2), music (day 3), etc. and 2) order 2 = no music (day 1), music (day 2), no music (day 3), etc (see Table below). ***Rationale:*** By using a crossover design, each subject was able to serve as his/her own control and compensate for potential improvement over time.

Table 1: Music Intervention Table

Orders	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Order 1	Music	No music	Music	No music	Music	No music
Order 2	No music	Music	No music	Music	No music	Music

4.2 SETTING AND SAMPLE

Subjects were recruited from patients admitted to a 30-bed LTACH that specializes in complex respiratory and wound care. Patients were admitted to this facility when their episode of critical

illness stabilized, but continued high acuity care and/or intensive rehabilitation were required. Approximately 20-50% patients were admitted due to inability to wean from mechanical ventilation. ***Rationale:*** At the time of LTACH admission, subjects have recovered from the more acute phase of critical illness and care focuses on weaning from mechanical ventilation.

A convenience sampling procedure was used to recruit subjects. Inclusion criteria were: 1) on mechanical ventilator for > 4 days (meets definition of PMV); 2) undergoing daily weaning trials (to permit daily data collection); 3) >21 years of age (no children enrolled); 4) no evidence of delirium (unable to evaluate effect on anxiety or shortness of breath if delirious); 5) able to listen to music (hearing loss limits benefit of music).

4.3 MEASUREMENTS

Physiologic parameters: HR, RR, SpO_2 & BP were recorded from the bedside monitor at 10 minute intervals for 90 minutes during music and non-music days. Mean artery pressure (MAP) was calculated from systolic and diastolic values using the standard formula.

Dyspnea and anxiety: Anxiety and dyspnea were assessed using a single-item visual analog scale (VAS) in the form of a vertical 100mm line. The bottom of the scale was anchored with a score of “0” by the statement “not anxious” or “no shortness of breath” and the top was anchored with a score of “100” by the statement “extremely anxious” or “extreme shortness of breath”. Patients were shown a VAS for anxiety (VAS-A) and dyspnea (VAS-D) at 30 minutes intervals (baseline, 30 minutes, 60 minutes and 90 minutes) and asked to provide a rating by pointing to the vertical line. VAS has been shown to be an accurate and sensitive tool to rate

subjective symptoms (L. L. Chlan, 2004). In prior studies in mechanically ventilated patients, VAS ratings have been shown produce reliable measures of anxiety (Knebel, Janson-Bjerklie, Malley, Wilson, & Marini, 1994) and to be moderately correlated (r=.49) with scores on the Spielberger State Anxiety Inventory, a well validated instrument used to assess state and trait anxiety (L. L. Chlan, 2004).

Daily weaning duration: was recorded as hours off mechanical ventilation during weaning trials. The decision to end daily trials was made by the respiratory therapist.

Delirium: Richmond Agitation-Sedation Scale (RASS) and Confusion Assessment Method for the ICU (CAM-ICU) were used to assess presence of delirium. First, level of consciousness was determined using the RASS. Patients who had RASS scores of -3 to +3 were next assessed using the CAM-ICU, a commonly used tool to assess delirium (McNicoll, Pisani, Ely, Gifford, & Inouye, 2005). The assessment involves asking patients to perform nonverbal tasks, answer simple yes/no logic questions and perform simple commands that replicate the CAM algorithm (McNicoll et al., 2005). The CAM-ICU is designed to identify 4 features of delirium: 1) acute onset of change or fluctuations in the course of mental status; 2) inattention; 3) disorganized thinking; and 4) an altered level of consciousness. Delirium is judged to be present if features 1 and 2 and either 3 or 4 are present (McNicoll et al., 2005). The CAM-ICU can be administered in < 4 minutes. The CAM-ICU is valid, and shows high inter-rater reliability (kappa = 0.79-0.96) (J. Tate & Happ, 2012). It demonstrated a sensitivity of 93% to 100% and specificities of 89 -100% when used by staff nurses (Ely et al., 2001).

Music assessment tool: Music preference was assessed using a 13-item tool that consists of yes/no questions, checklists and open-ended questions to guide music preference assessment. The tool was developed by Chlan (L. Chlan & Heiderscheit, 2009) and has been extensively used

for this purpose in mechanically ventilated patients (L. L. Chlan et al., 2013; Heiderscheit, Breckenridge, Chlan, & Savik, 2014). Patients were asked to identify their favorite type of music (classical, country music, jazz, etc.), favorite musician, preferred instruments (guitar, vocal, piano, etc) as well as music and/or instruments they did not like. Based on a review of studies, Tang (2010) concluded that relaxing music is composed primarily of string compositions, low pitched sounds, a simple and direct rhythm and a temp of approximately 60-70 beats per minute. Permission for use was granted by the author.

Demographic and medical condition data were collected from the medical record including age, race, gender, primary diagnosis, pre-intervention LTACH length of stay, and Acute Physiology and Chronic Health Evaluation III (APACHE III) score.

4.4 RECRUITMENT

The PI requested an IRB waiver to screen subjects for study entry. When eligible subjects were identified, a member of the patient care team was asked to inform the patient about the study and, if interested, requested permission for the PI to contact the patient and explain the study's purpose, benefits and risks. Eligible subjects were informed about the study, its risks and benefits and assured that participation was voluntary and that confidentiality was maintained. If willing to participate, eligible subjects or their family member were asked to sign a consent for participation.

Prior to data collection

1. The PI confirmed that the subject met eligibility criteria and informed consent was obtained. After consent, subjects were randomized by asking them to select a card with the order noted from an envelope. If unable to do this, a surrogate selected the card.
2. After randomization, the subject was assisted to complete the music assessment tool or, if unable to do this, input was provided by a family member. After selection was completed, subjects were asked to listen to selected songs recorded on a MP3 player for a short interval to confirm their selection.

Data collection days

3. On data collection days, the PI assessed sedation level and presence of delirium. Richmond Agitation Sedation Scale (RASS) (Sessler et al., 2002) and the Confusion Assessment Method for the ICU (CAM-ICU) were used to assess sedation level and delirium respectively (McNicoll et al., 2005). Subjects were not eligible to participate if delirium was present (unable to evaluate effect of intervention).
4. During weaning trials on music listening days, data were collected (see independent variable) for 30 minutes. Headphones were then applied with patient selected music for 60 minutes during the weaning trial (total data collection time 90 minutes). On non-music days, the same data were collected for 90 minutes. ***Rationale:*** prior studies have used times ranging from 20-120 minutes; the proposed duration of 60 minutes, a midpoint, allows evaluation of effect before and during the weaning trial. On both days, the environment was controlled to the extent possible by dimming lights and posting a 'please do not disturb' sign. Nurses and medical staff were instructed to limit care

interruptions unless required during the intervention period. Patients were instructed to lie quietly with their eyes closed, rest and think of something pleasant.

5. If a change in condition required that weaning trials be postponed for one or more days, subjects were retained in the study and the intervention continued after weaning trials resumed unless the number of days without trials exceeded 4 days.
6. Because subjects were recruited from a LTACH, their condition was more stable and therapy was targeted to achieve weaning success, we expected few interruptions in daily scheduled weaning trials. The music intervention was terminated if any of the following occurred: HR >140 beats/minute, RR >35 minute, systolic BP >180 mm Hg or < 90mm Hg, or respiratory distress evidenced by agitation or perspiration.

4.5 DATA ANALYSIS

Data analysis was conducted using SAS software, version 9.4 (SAS Institute, 2015). Descriptive statistics were used to summarize demographic and medical condition data. Mean values was calculated for the first 30 minutes (PRE) and the following 60 minutes (POST) for each outcome variable (HR, RR, MAP, SpO_2, VAS-A, and VAS-D). Paired student t-tests were used to compare mean pre/post differences in physiologic variables (HR, RR, MAP, SpO_2) and VAS-A and VAS-D within music and no music days. Paired student t-tests were also used to compare mean differences in these variables and daily weaning duration between music and no music days. In addition, a multivariate mixed-effects model analysis (using the MIXED Procedure in SAS) was used to capture the longitudinal repeated outcome measures and compare mean

differences. A multivariate mixed-effect model utilizes all data points in the model; missing data is handled by specifying an appropriate covariance structure.

5.0 SUMMARY OF FINDINGS

When comparisons were made pre and post intervention on music days, there were significant decreases in HR, RR, anxiety (VAS-A), and dyspnea (VAS-D) ($p<0.05$), but not SpO_2 or BP. There were no significant changes for the above variables on non-music days. When comparisons were made between mean values for the 3 music and 3 non-music days, there were significant decreases in RR, dyspnea (VAS-D) and total weaning time ($p<0.05$). A multivariate mixed-effects model analysis demonstrated significant decreases in HR, RR, VAS-A, and VAS-D and a significant increase in daily weaning duration on music days ($p<0.05$). Providing patient selected music was a simple, potentially beneficial intervention for LTACH patients during daily weaning trials. Further study is indicated to test ability of this intervention to promote weaning success and benefit earlier in the weaning process.

6.0 STUDY RESULTS

Findings of this study are presented in the format of manuscript to be submitted to the journal Critical Care Medicine. A future manuscript will include discussion of ways to implement this intervention in clinical practice.

APPENDIX A IRB APPROVAL LETTER

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Zhan Liang RN BSN
From: IRB Office
Date: 8/26/2014
IRB#: REN14080148 / PRO11080650
Subject: Effect of Music Intervention on Weaning From Prolonged Mechanical Ventilation

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Your renewal for the above referenced research study has received expedited review and approval from the Institutional Review Board under:
45 CFR 46.110.(4)
45 CFR 46.110.(5)
45 CFR 46.110.(7)

Please note the following information:

Approval Date: 8/26/2014
Expiration Date: 9/12/2017

This study meets the criteria for an extended approval period of three years. In the event that any type of federal funding is obtained during this interval, a modification must be submitted immediately so the IRB can reassess the approval period.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least **one month** prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.

APPENDIX B QUESTIONNAIRES

IRB: PRO11080650
PI: Zhan Liang, RN, BSN **Mentor:** Leslie Hoffman, PhD, RN
Study Title: Effect of Music Intervention on Weaning From Prolonged Mechanical Ventilation
Subject ID: _____

Demographic Questionnaire

1. Age: _____

2. Gender:

☐ **Male**

☐ **Female**

3. Educational Level:

☐ **Primary and lower**

☐ **Secondary**

☐ **College and higher**

4. Race: _____

5. Primary Diagnosis: _____

6. Reason for Admission: _____

7. ICU Admission Date: _____

8. ICU Discharge Date: _____

9. APACHE II at Enrollment: _____

10. Ventilator Mode: ☐ **SIMV** ☐ **Other**

IRB: PRO11080650
PI: Zhan Liang, RN, BSN **Mentor:** Leslie Hoffman, PhD, RN
Study Title: Effect of Music Intervention on Weaning From Prolonged Mechanical Ventilation
Subject ID: _____

DAY: _____ **Visit Date:** _____ **Music Intervention:** ☐ **Music** ☐ **No Music** **CAM-ICU:** ☐ **Yes** ☐ **No** **RASS:** _____ **Weaning Trial Duration:** _____ **Sedative Drug** _____										
Procedures	**Prior WT**	**30 Minutes With Headset During WT**			**60 Minutes with Headset DURING WT**					
Minutes	**0**	**10**	**20**	**30**	**10**	**20**	**30**	**40**	**50**	**60**
Time										
HR										
SpO_2										
RR										
BP										
Anxiety										
SOB										

Patient – Visual Analog Scale – Dyspnea

Patient Study Code_____ Date/Time_____

Please rate your shortness of breath by placing a mark on scale below bounded at the bottom by "no shortness of breath" and on the top by "worst shortness of breath possible."

100	**Worst shortness of breath possible**
90	
80	
70	
60	
50	
40	
30	
20	
10	
0	**No shortness of breath**

Patient – Visual Analog Scale – Anxiety

Patient Study Code_____ Date/Time_____

Please rate your anxiety by placing a mark on scale below bounded at the bottom by “no anxiety” and on the top by “worst anxiety possible”.

100	**Worst anxiety possible**
90	
80	
70	
60	
50	
40	
30	
20	
10	
0	**No anxiety**

APPENDIX C HUMAN SUBJECTS

Human Subjects

Human Subjects Involvement and Characteristics, and Design

The study used a prospective crossover pre-post repeated measures design. Inclusion criteria were: 1) on mechanical ventilator for > 4 days (meets definition of PMV); 2) undergoing daily weaning trials (to permit daily data collection); 3) >21 years of age (no children enrolled); 4) no evidence of delirium (unable to evaluate effect on anxiety or shortness of breath if delirious); 5) able to listen to music (hearing loss limits benefit of music). The study goal was to enroll patients with an approximate age of 60 ± 18 years based on prior studies in the same setting (L. L. Chlan et al., 2013; Happ et al., 2011).

A convenience sampling procedure was used. Subjects were randomized into two different music intervention orders for 6 consecutive days during their scheduled weaning trials. Data collection continued for 6 days. Demographic data was extracted from the medical record. Patients were assessed their music preference using the Music Assessment Test and their delirium status was assessed using the RASS and CAM-ICU (to rule out delirium). Physiologic data was obtained from the bedside monit*or*. Dyspnea and anxiety level were assessed using visual analog scale (VAS).

Recruitment

Approval was obtained from the IRB to conduct the study (Appendix A). The PI requested an IRB waiver to screen subjects for study entry. Rationale for an IRB screen waiver was that patient information was accessible to the unit staff who could therefore screen potential subjects using data from the medical record.

When potentially eligible subjects were identified, a member of the patient care team was asked to inform the patient about the study and, if interested, requested permission for the PI to contact the patient and explain the study's purpose, benefits and risks. Eligible subjects were informed that participation in this study was completely voluntary, they may refuse to participate in it or withdraw at any time even after signing informed consent and their decision to not participate in the study would not affect their relationship with or the care received from hospital.

Protection against Risks

No risks associated with use of music as an intervention have been reported in previous studies. To protect against risk, the PI used the following criteria to determine need to stop the intervention: an increase of HR (>140 beats/minute) or RR (>35 breathings/minute), blood pressure (systolic BP >180 mmHg or < 90mm Hg), ventilation problems, agitation or perspiration. In addition, the PI also stopped the intervention on patient request.

Measurement of physiological parameters and sedation scores were part of routine ICU care; consequently no additional burden was placed on the patients.

To protect confidentiality of study data, the PI assigned a coded identification number to all participant data obtained from study instruments or abstracted from the medical record. Each patient was assigned a coded identification number and data were stored in a locked file cabinet. The form, which identified the patients by code number, was kept in a separate area from study data.

Potential Benefits

Possible benefits of the study included a decrease in anxiety and shortness of breath and potentially a decrease ventilator weaning days. It was hoped that the music intervention, if found effective, would be used in LTACH and benefit mechanically ventilated patients. It was also possible that patients will receive no benefit from the study.

Inclusion of women and minorities

In prior studies conducted in this setting, the gender distribution of subjects was 53% female and 13% African American (Happ et al., 2011). We anticipated a patient sample with the same gender and minority distribution.

Inclusion of children

To enroll in the study, subjects must be >21 years of age. Therefore, the study did not enroll children. Patients less than or equal to 21 years of age would be unlikely to require PMV and, if required, this would be an unusual case.

Data & Safety Monitoring Plan

Data and safety monitoring was conducted during monthly meetings with Co-Investigators (Drs. Hoffman and Ren) during which data acquisition, management and any adverse events arising from the study will be reviewed. A summary of these reviews was provided to the IRB at the time of the yearly renewal. Any unanticipated adverse events were reported immediately to the IRB.

APPENDIX D MANUSCRIPT

Manuscript Reporting Dissertation Findings

Effect of Music Intervention during Weaning Trials in a Long

Term Acute Care Hospital – A 6 Day Prospective Randomized Crossover Trial

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Reprints not requested

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Research Award

Keywords: music intervention; weaning; long term acute care hospital, mechanical ventilation

Abstract

Objective: To examine the effect of patient-selected music intervention during daily weaning trials for patients on prolonged mechanical ventilation.

Design: Randomized crossover repeated measures design.

Setting: Long-term acute care hospital.

Patients: Patients on mechanical ventilation for ≥ 4 days undergoing daily weaning trials.

Intervention: Patients were randomized to patient-selected music vs no music on the first day of the intervention; provision of music was alternated for 6 days, resulting in 3 music and 3 no music days for each patient. During weaning trials on music days, data were obtained for 30 minutes prior to music listening and continued for 60 minutes while patients listened to selected music (total 90 minutes). On no music days, data were collected for 90 minutes.

Measurements and Main Results: Outcome measures included heart rate (HR), respiratory rate (RR), arterial oxygenation (SpO_2), blood pressure (BP), dyspnea and anxiety assessed with a visual analog scale (VAS-D, VAS-A) and daily weaning duration (hours). Of 31 patients enrolled, 23 completed the 6-day intervention. Patients were 61.6 ± 10.9 years of age, 74% male, and 96% white. A multivariate mixed-effects model analysis demonstrated significant decreases in HR, RR, VAS-A, and VAS-D and a significant increase in daily weaning duration on music days ($p<0.05$).

Conclusion: Providing patient selected music is a simple, potentially beneficial intervention for LTACH patients during daily weaning trials. Further study is indicated to test ability of this intervention to promote weaning success in LTACH patients and benefits earlier in the weaning process.

Introduction

Prolonged mechanical ventilation is a major concern to patients, caregivers, and clinicians (Carson et al., 2012; Hermans et al., 2014; Herridge et al., 2011; Leroy, Devos, Lambiotte, Thevenin, & Leroy, 2014). By 2020, the number of patients who require prolonged mechanical ventilation is projected to reach 600,000 cases in the United States and account for nearly two-thirds of the cost for all resources devoted to mechanical ventilation (Zilberberg, de Wit, & Shorr, 2012; Zilberberg, Luippold, Sulsky, & Shorr, 2008). Among strategies tested to achieve liberation from mechanical ventilation, weaning protocols and approaches incorporated in the ABCDE (awakening, breathing, delirium management, early exercise/mobility) bundle have been shown to improve patient outcomes, including weaning success, in the intensive care setting (Balas et al., 2013; Blackwood et al., 2011; Nichols & O'Rourke, 1988). When these strategies are not successful, patients may be transferred to a rehabilitation focused setting, such as a long-term acute care hospital, to complete the weaning process.

Long-term acute care hospitals (LTACH) provide complex inpatient care for patients in the recovery phase of illness and are among the fastest growing and highest paid providers of post-acute care in the United States (Kahn et al., 2013; Kim et al., 2015). A number of studies have examined outcomes of mechanically ventilated patients admitted to a LTACH, but the majority are descriptive (Dermot Frengley, Sansone, Shakya, & Kaner, 2014; Kahn, Benson, Appleby, Carson, & Iwashyna, 2010; Scheinhorn et al., 2007; Seneff et al., 2000). Although many studies have tested interventions to promote weaning in the intensive care setting, evidence regarding best strategies in a LTACH setting is limited to one study (Jubran et al., 2013).

Patients who require prolonged mechanical ventilation are at high risk of psychological morbidity (Bradt et al., 2015; Kim et al., 2015; Nelson et al., 2004). From a study of 50 patients who were transferred to a respiratory care unit for weaning from prolonged mechanical ventilation, Nelson and colleagues (2004) found that over 60% reported dyspnea during weaning. More than 60% also reported psychological symptoms "frequently" or "almost constantly." In this situation, weaning trials may exacerbate symptoms, resulting in early termination of the trial and prolong need for support. We therefore reasoned that a strategy targeted at reducing stress during weaning might be especially beneficial in this setting.

Music is a non-pharmacologic intervention that can be used as a complementary adjunct in the care of patients supported by mechanical ventilation (Chan, Chung, Chung, & Lee, 2009). Music is a distracting agent that refocuses attention and influences emotions. Music may also promote relaxation via biologic mechanisms that include a reduction in blood cortisol (Beaulieu-Boire et al., 2013; Tracy & Chlan, 2011). Prior studies report that music intervention can relieve pain and anxiety and increase comfort in patients admitted to an intensive care unit (Bradt & Dileo, 2014; Chan et al., 2009; L. L. Chlan et al., 2013; Han et al., 2010; Hunter et al., 2010; Korhan, Khorshid, & Uyar, 2011). A recent Cochrane review concluded that listening to music consistently reduced respiratory rate, systolic blood pressure, and had an anxiety-reducing effect in mechanically ventilated patients (Bradt & Dileo, 2014). In this review, which included 14 clinical trials (805 patients on mechanical ventilation), music listening resulted in a reduction in anxiety that, on average, was 1.11 standard deviation units greater (95% CI -1.75 to -0.47, $p = 0.0006$) than usual care.

We were able to identify only one study that tested music intervention as a means to promote weaning from mechanical ventilation (Hunter et al., 2010). In this study, 51 patients

listened to music for 40-60 minutes during weaning trials three times a week. Findings showed a significant reduction in respiratory rate, heart rate and increased patient satisfaction ($p<0.05$), but the comparison was to a retrospective sample. No studies were identified that tested effects of music intervention to promote weaning in a LTACH. Thus, the purpose of this study was to explore the effect of a music intervention on selected physiologic variables, dyspnea, anxiety and daily weaning duration in patients undergoing daily weaning trials in a LTACH.

Material and Methods

Study Design

The study used a prospective crossover repeated measures design. Patients were randomized into 2 music intervention orders for 6 days during their scheduled weaning trial with use of music alternated each day: 1) order 1 = music (day 1), no music (day 2), music (day 3), etc. and 2) order 2 = no music (day 1), music (day 2), no music (day 3), etc. The rationale for using this design was to allow each subject to serve as his/her own control and compensate for potential improvement over time.

Setting and Sample

Patients were recruited from a 30-bed LTACH that specializes in complex respiratory and wound care. Patients were eligible for the study if they were 1) on mechanical ventilation for ≥ 4 days (meets definition of prolonged mechanical ventilation); 2) undergoing daily weaning trials (to permit daily data collection); 3) ≥ 21 years of age (no children enrolled); 4) no evidence of delirium (assessed using the Richmond Agitation Sedation Scale [RASS] and Confusion Assessment Method for the ICU [CAM-ICU]) (McNicoll et al., 2005; Sessler et al., 2002); 5) able to listen to music via headphones (hearing loss limits benefit). The study was approved by

the University of Pittsburgh Institutional Review Board and all patients provided informed consent.

Measurements

Demographic and clinical data were collected from the medical record including age, race, gender, primary diagnosis, LTACH length of stay prior to entering the study, and Acute Physiology and Chronic Health Evaluation III (APACHE III) score.

Physiologic parameters: Heart rate (HR), respiratory rate (RR), oxygen saturation (SpO_2) and blood pressure (BP) were recorded from the bedside monitor at 10-minute intervals for 90 minutes during music and no-music days. Mean arterial pressure (MAP) was calculated from systolic and diastolic values using the standard formula (Nichols & O'Rourke, 1988).

Dyspnea and anxiety were assessed using a single-item visual analog scale (VAS) in the form of a vertical 100mm line. The bottom of the scale was anchored with a score of "0" by the statement "not anxious" or "no shortness of breath" and the top was anchored with a score of "100" by the statement "extremely anxious" or "extreme shortness of breath". Patients were asked to provide a rating by pointing to the vertical line on the VAS questionnaire for dyspnea (VAS-D) and anxiety (VAS-A) at 30 minute intervals (baseline, 30 minutes, 60 minutes and 90 minutes). VAS is an accurate and sensitive tool to rate subjective symptoms (L. L. Chlan, 2004). In prior studies in mechanically ventilated patients, VAS ratings proved to be reliable measures of anxiety (Knebel et al., 1994) and were moderately correlated (r=.49) with scores on the Spielberger State Anxiety Inventory, a well validated instrument used to assess anxiety (L. L. Chlan, 2004).

Daily weaning duration was recorded as hours off mechanical ventilation during daily weaning trials. The decision to end weaning trials was made by the respiratory therapist.

Music assessment tool: Music preference was assessed using a 13-item tool consisting of yes/no questions, checklists, and open-ended questions. The tool was developed by Chlan and Heiderscheit (2009) and has been used extensively for this purpose in mechanically ventilated patients (L. L. Chlan et al., 2013; Heiderscheit et al., 2014). Patients were asked to identify their favorite type of music (classical, country music, jazz, etc.), favorite musician, preferred instruments (guitar, vocal, piano, etc) as well as music and/or instruments they disliked. Music with a range of 60-80 beats per minute is most commonly used as it mimics the adult human HR (Tracy & Chlan, 2011). Selections were made that matched this criteria and patient preferences. Permission for tool use was granted by the author.

Data collection

Eligible patients were identified by LTACH staff. The study and its risks and benefits were described by a member of the research team and consent obtained. If patients were unable to sign the consent, a surrogate was asked to sign for the patient. Patients were then randomized by asking them to select a card with the order noted from an envelope. If unable to do this, a surrogate selected the card. After randomization, the patient was assisted to complete the music assessment tool or, if unable to do this, input was provided by a family member. After selection was completed, patients were asked to listen to selected songs recorded on a MP3 player to confirm their selection.

During weaning trials on music listening days, data were collected (HR, RR, SpO_2, BP, VAS-A, VAS-D) for 30 minutes. Headphones were then applied with patient selected music for 60 minutes during the weaning trial (total data collection 90 minutes). On no-music days, the same data were collected for 90 minutes. On both days, the environment was controlled to the extent possible by dimming lights and posting a ‘please do not disturb’ sign. Nurses and medical

staff were instructed to limit care interruptions during the intervention period. Patients were instructed to lie quietly with their eyes closed, rest and think of something pleasant. If a change in condition required that weaning trials be postponed for one or more days, patients were retained in the study and the intervention continued after weaning trials resumed unless the number of days without weaning trials exceeded 4 days. The music intervention was terminated if any of the following occurred: HR >140 beats/minute, RR >35 minute, systolic blood pressure >180 mmHg or < 90mmHg, or respiratory distress evidenced by agitation or perspiration. At the end of 90 minutes, the weaning trial continued with trial duration determined by the respiratory therapist.

Data analysis

Data analysis was conducted using SAS software, version 9.4 (SAS Institute, 2015). Descriptive statistics were used to summarize demographic and medical condition data. Mean values was calculated for the first 30 minutes (PRE) and the following 60 minutes (POST) for each outcome variable (HR, RR, MAP, SpO2, VAS-A, and VAS-D). Paired student t-tests were used to compare mean pre/post differences in physiologic variables (HR, RR, MAP, SpO_2) and VAS-A and VAS-D within music and no music days. Paired student t-tests were also used to compare mean differences in these variables and daily weaning duration between music and no music days. In addition, a multivariate mixed-effects model analysis (using the MIXED Procedure in SAS) was used to capture the longitudinal repeated outcome measures and compare mean differences. A multivariate mixed-effect model utilizes all data points in the model; missing data is handled by specifying an appropriate covariance structure. Statistical significance was defined as $p \leq 0.05$. A post-hoc power analysis using the current sample size of 23 patients demonstrated

99% power and an effect size of 1.5 with a mean difference of 3.1 and standard deviation of the paired difference of 3.0 (one of the main outcome values: RR).

Results

Demographic and clinical data

Of the 41 patients approached, 10 refused to participate, and the remaining 31 were randomized into the two orders (Figure 2). Three were withdrawn after 1 day due to patient request or deterioration in condition, and 5 were withdrawn after 2-5 days for the same reason, leaving 23 who completed the 6-day intervention and remained for data analysis. Patients were 61.6 ± 10.9 years of age, 74% male, 96% white, with a 16.5 ± 20.0 day LTACH stay prior enrollment. The most prevalent admission diagnosis was of a pulmonary etiology, followed by neurologic. There were no significant differences between patients randomized to the two orders (music vs no music) (Table 2).

Pre/post comparison within music and no-music days

When comparisons were made pre and post intervention within music days for patients who completed the 6-day intervention (n=23), there was a significant decrease in HR, RR, VAS-D, and VAS-A ($p<0.05$) (Table 3). There were no significant differences for these variables on no-music days.

Comparison between music days and non-music days

When comparisons were made between the 3 music and 3 no-music days for patients who completed the 6-day intervention (n=23), there were significant decreases in RR and VAS-D and a significant increase in daily weaning duration ($p<0.05$) (Table 4).

Pattern of daily change in 6 day music intervention

Figure 3 presents the pattern of change for HR, RR, VAS-A and VAS-D during the 6-day data collection period. The majority of change occurred on Day 2 of the music intervention (HR, RR, VAS-A and VAS-D) and continued for RR, VAS-A and VAS-D.

Multivariate mixed-effect model for all outcomes measures

For the 23 patients, a multivariate mixed-effect model analysis showed a significant decrease in HR, RR, VAS-A, VAS-D and a significant increase in daily weaning duration (Table 5). Significant changes were not seen for SpO_2 or MAP. Figure 4 presents the adjusted mean change between music days and no music days. When the mixed-effect model analysis was repeated for a sample of 28 patients (including those who completed $\geq$ 2 days of the intervention), the results were consistent with the 23 subjects who completed 6-day intervention (Table 6)

Discussion

The major finding of our study was that patient-selected music intervention decreased dyspnea and anxiety and increased daily weaning duration for prolonged mechanical ventilated patients during daily weaning trials. The strengths of our study include use of a prospective randomized cross-over design, a longer duration of the music intervention period (6 days), the study setting, and demonstration of adequate statistical power. To our knowledge, this is the first randomized controlled trial to examine effects of music intervention on weaning from prolonged mechanical ventilation in a LTACH setting.

The priority when managing the care of mechanical ventilated patients is to initiate weaning trials as soon and as safely as possible. When duration of ventilator dependency is prolonged, patients may be transferred to a LTACH for continuing weaning and rehabilitation. The frequency of transferring patients to LTACHs varies regionally, but appears to be

increasing. For example, in a retrospective cohort study, Kahn and colleagues (2010) reported that LTACH admissions increased from 13,732 in 1997 to 40,353 in 2006, with a concurrent increase in the proportion of those who required mechanical ventilation (16.4% vs. 29.8%). Despite increasing use of LTACH as a post-acute care option, few studies have tested ways to optimize care in this setting.

We were only able to identify one randomized controlled trial that evaluated ways to promote weaning from mechanical ventilation in a LTACH. In this study, which compared use of pressure support and unassisted breathing through a tracheostomy during weaning trials, Jubran and colleagues (Jubran et al., 2013) found that unassisted breathing resulted in a shorter median weaning time. In addition, Jubran and colleagues (2010) reported that, of 336 prolonged mechanical ventilated patients admitted to a LTACH who were sufficiently alert to be interviewed by a clinical psychologist, 42% had depressive disorders. Patients with depressive disorders were more likely to experience weaning failure than those without (61% vs 33%, p=.0001). We therefore reasoned that an intervention targeted at reducing anxiety and dyspnea might benefit LTACH patients.

Our study showed significant decreases in HR, RR, anxiety, and dyspnea and a significant increase in daily weaning duration with the multivariate mixed-effect model analysis. Our findings were consistent with prior studies testing benefits in critically ill patients (Bradt & Dileo, 2014; Chan et al., 2009; L. L. Chlan et al., 2013; Han et al., 2010; Hunter et al., 2010; Korhan et al., 2011; Lee et al., 2005). In a randomized clinical trial that enrolled 373 mechanically ventilated patients from 12 ICUs, a patient directed music intervention resulted in greater reduction in anxiety, sedation frequency and sedation intensity compared to a noise control and usual care group (L. L. Chlan et al., 2013). Lee and colleagues (2005) reported a

significant reduction in HR, RR, systolic and diastolic BP ($p<0.05$) when music was administered for the same interval compared to controls (no music) in 64 mechanically ventilated patients. However, these studies were conducted in settings where patients were more acutely ill. Our study adds to the literature by examining effects of music intervention in a LTACH setting.

There are several explanations for the beneficial effects of music. It has been proposed that benefit results from suppressive action on the sympathetic nervous system, leading to decreased adrenergic activity. Potentially, music may also trigger the limbic system in the brain to release endorphins, neurotransmitters that play an important role in enhancing a sense of well-being (Koelsch, Fritz, Schulze, Alsop, & Schlaug, 2005; Menon & Levitin, 2005). Beaulieu-Boire and colleagues (2013) tested two 1-hour daily periods of music-vs-sham-MP3 listening in 49 sedated mechanically ventilated patients. They reported a significant decrease in cortisol and prolactin blood concentrations and a significant increase in adrenocorticotrophic hormone (ACTH)/cortisol ratio during music listening compared with sham MP3 listening. These findings suggest a potential mechanistic explanation for the effect of music intervention.

Additional factors that may explain response include the patient's preference for music as a relaxation modality (Bradt & Dileo, 2014). In our study, 25% of those approached refused participation and additional subjects withdrew after several days of participation, suggesting preference is an important factor. Nevertheless, the intervention is low cost, without adverse effects, and appears an excellent option to offer as a relaxing agent.

In our participants, the majority of improvement occurred during the second day of the music intervention (HR, RR, MAP, anxiety and dyspnea). Positive changes continued through the third day for some variables, such as RR, anxiety and dyspnea. While most previous studies provided music intervention for one or two days (L. L. Chlan et al., 2007; Conrad et al., 2007;

Korhan et al., 2011; Phipps, Carroll, & Tsiantoulas, 2010; Wong et al., 2001), a randomized controlled trial by Chlan and colleagues (2013) provided a patient directed music intervention at least twice daily up to 30 days as long as patients were receiving ventilator support. Results demonstrated that the patient directed music intervention lowered anxiety level consistently by 19 points during the observation period. Future studies should test benefits for a longer interval and include biological markers of stress (e.g., cortisol, prolactin, etc.) and assess depression prevalence to better explain the mechanism of music intervention for stress responses and to confirm benefits of music intervention.

Limitations

The study was done in one LTACH which might limit the generalizability of the study. Also, we did not assess weaning success or other variables that may influence study outcomes, e.g, use of pain/anxiety medication, depression. The study was not guided by a professional music therapist. Prior studies indicate participants may experience greater benefit when music intervention is led by a trained music therapist (Bradt et al., 2015). However, our significant results, even in the absence of a trained therapist, suggest that some benefit can still be realized. Whether this benefit would be greater with a therapist is possible.

Conclusion

Patients who require prolonged mechanical ventilation are at high risk for psychological morbidity. Our study demonstrated that music intervention, provided to patients undergoing weaning trials in a LTACH, resulted in significant changes in physiologic variables and perceptions of anxiety and dyspnea and an increase in weaning trial duration. Having patients listen to their choice of music during daily weaning trials could benefit patients and may speed

liberation from mechanical ventilation. Further study is indicated to test ability of this intervention to promote weaning success and benefit earlier in the weaning process.

Acknowledgement:

We want to acknowledge Michael P. Donahoe, MD for his support of the study and Linda L. Chlan, PhD, RN for generously sharing the music assessment tool. In addition, we wish to acknowledge Dr. Chaohsing Yeh and Dr. Rosemary Hoffmann for their contributions during review of study findings.

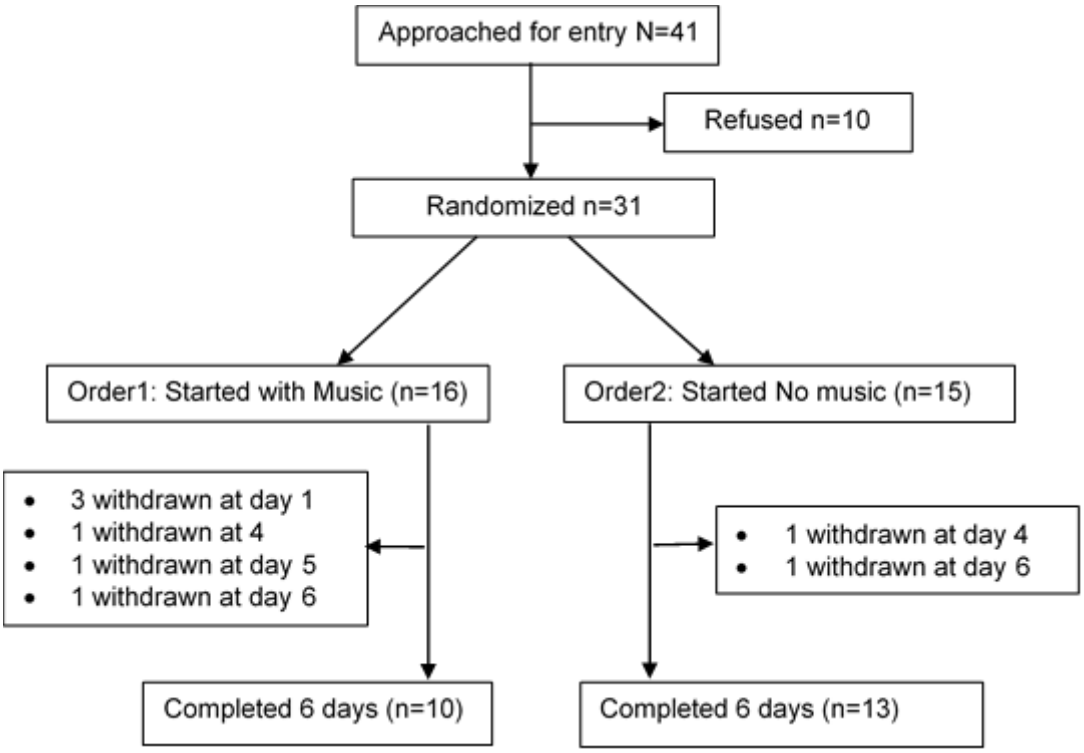

Figure 2. Subject Flow Chart

Table 2: Demographic and Clinical Data (n=23)

	Completed 6 days	Started with Music	Started with No music	P-value
	N=23	N=10	N=13	
Age, years	61.6 ± 10.9	62.5 ± 7.8	60.9 ± 13.1	0.74
Male n, (%)	17 (73.9)	8 (80)	9 (69.2)	0.56
Caucasian n, (%)	22 (95.7)	10 (100)	12 (92.3)	0.37
Admission Diagnosis n, (%)				0.64
Pulmonary	17 (73.9)	8 (80)	9 (69.2)	
Cardiac	1 (4.3)	0	1 (7.7)	
Neurological	4 (17.4)	2 (20)	2 (15.4)	
Gastrointestinal	1 (4.3)	0	1 (7.7)	
Pre-intervention LOS, days	16.5 ± 20.0	23.8 ± 28.2	10.9 ± 7.4	0.13
APACHE III score	48.4 ± 14.5	47.4 ± 11.8	49.2 ± 16.7	0.78

Table 3: Pre-post Comparison within Music and No-music days (n=23)

	Music Days			No music Days		
	Pre	Post	P-value	Pre	Post	P-Value
HR	86.8 ±18.0	84.3 ± 17.9	**<0.01**	86.4 ± 19.0	85.9 ± 18.8	0.51
SpO_2	97.0 ± 2.5	97.0 ± 2.7	0.53	97.4 ± 2.3	97.5 ± 2.2	0.78
RR	24.7 ± 5.6	21.5 ± 6.5	**<0.01**	24.3 ± 5.8	24.0 ± 6.3	0.53
MAP	85.8 ± 7.9	85.2 ± 8.4	0.40	85.8 ± 9.3	85.9 ± 8.5	0.87
VAS-A	28.5 ± 26.0	21.5 ± 22.4	**<0.01**	29.4 ± 26.0	26.7 ± 24.1	0.19
VAS-D	25.3 ± 27.0	18.2 ± 22.7	**<0.01**	23.9 ± 25.6	23.9 ± 25.4	0.99

HR=heart rate; SpO_2 = oxygen saturation; RR=respiratory rate; MAP=mean artery pressure; VAS-A = visual analog scale for anxiety; VAS-D = visual analog scale for dyspnea.

Table 4: Comparison of Changes between Music and No-music Days (n=23)

Pre-Post Mean Difference	Music days	No Music days	P-Value
HR	-1.8 ± 2.1	-0.6 ± 2.5	0.11
SpO2	0.1 ± 1.0	-0.0 ± 0.9	0.78
RR	-3.1 ± 3.0	0.2 ± 1.9	**<0.01**
MAP	-0.59 ± 2.7	-0.1 ± 3.3	0.58
VAS-A	-7.0 ± 7.6	-2.7 ± 10.9	<0.10
VAS-D	-7.5 ± 9.3	-0.0 ± 10.1	**<0.01**
Daily weaning duration	18.3 ± 5.5	17.0 ± 6.1	**0.02**

HR=heart rate; SpO2= oxygen saturation; RR=respiratory rate; MAP=mean artery pressure; VAS-A = visual analog scale for anxiety; VAS-D = visual analog scale for dyspnea; Daily weaning duration =daily average time off ventilator measured in hours.

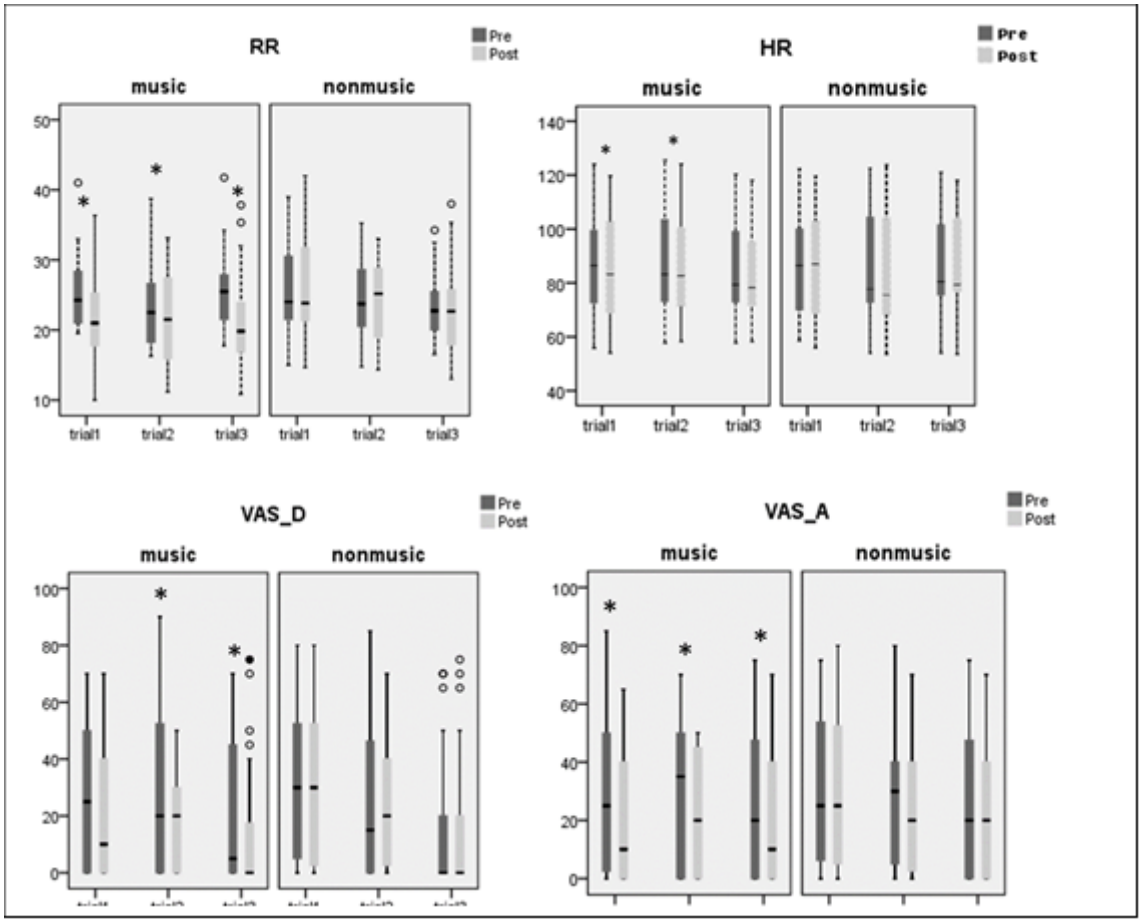

Figure 3. Pattern of Daily Change in Values for RR, HR, VAS-D, VAS-A during Daily Weaning Trials

Pre-trial values are indicated by dark bars and post-trial values grey bars. Significant changes are indicated was an asterisk ($p<0.05$).

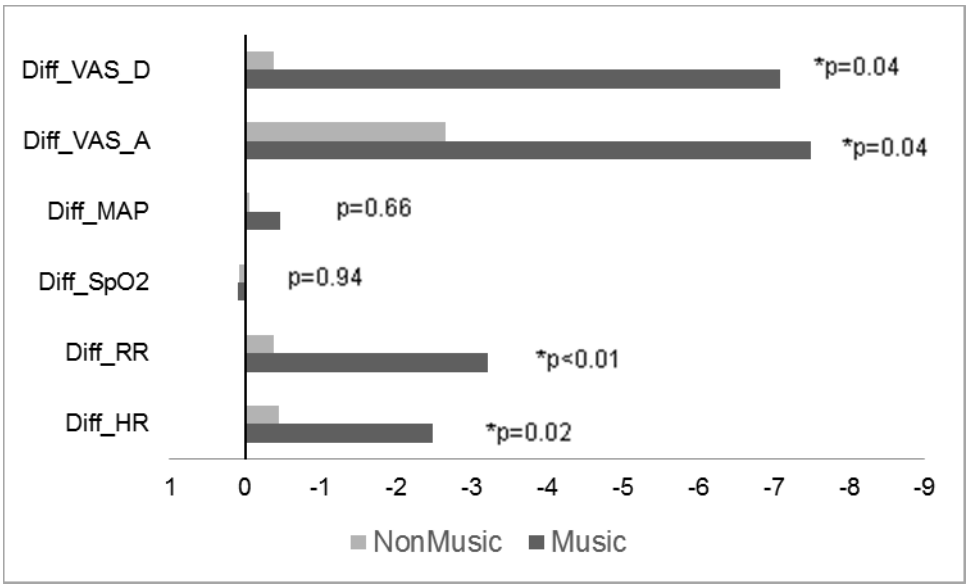

Figure 4. Adjusted Mean Change between Music and No-music Days Using Mixed-effect Model Analysis (n=23).

Values for differences (diff) were calculated by subtracting the value obtained prior to beginning the intervention from the value obtained following completion of the intervention for music (dark bar) and no music (grey bar) days. There was a significant decrease in visual analog scores for shortness of breath and anxiety (p=.04) and a significant decrease in respiratory rate (RR) (p <.01) and heart rate (HR) (p=.02) rate. Significant changes were not seen for mean arterial pressure (MAP) or arterial oxygen (SpO_2) values.

Table 5: Mixed-effect Model for All Outcome Measures (n=23)

		Diff_HR		Diff_SpO2		Diff_RR		Diff_MAP		Diff_VAS-A		Diff_VAS-D		Dailyweaningduration	
		Estimate	P	Estimate	P	Estimate	P	Estimate	P	Estimate	P	Estimate	P	Estimate	P
Treatment	Music	-2.04	**0.02**	0.02	0.94	-2.84	**<0.01**	-0.41	0.66	-4.83	**0.04**	-8.12	**0.04**	1.04	**0.05**
	No music	0	-	0	-	0	-	0	-	0	-	0	-	0	-
Order	1	0.43	0.72	-0.05	0.87	-1.85	0.03	-0.30	0.74	-3.55	0.17	-3.17	0.33	-0.43	0.86
	2	0	-	0	-	0	-	0	-	0	-	0	-	0	-
Overall p-value for day		-	0.78	-	0.62	-	0.17	-	0.15	-	0.2	-	0.42	-	<0.01
Day	1	0.35	0.93	0.12	0.77	0.12	0.91	2.60	0.11	-6.42	0.09	1.92	0.63	-5.26	<0.01
	2	0.02	0.91	-0.39	0.33	1.38	0.19	0.75	0.64	-2.74	0.47	5.10	0.20	-1.89	0.05
	3	-0.14	0.81	0.21	0.60	1.57	0.14	1.30	0.41	-5.47	0.15	2.32	0.56	-0.84	0.37
	4	-0.37	0.96	-0.29	0.48	1.47	0.16	0.26	0.87	-9.71	0.01	-2.24	0.57	-0.88	0.35
	5	1.51	0.3	-0.21	0.60	0.62	0.55	3.73	0.02	-7.70	0.05	-1.81	0.65	-0.75	0.42
	6	0	-	0	-	0	-	0	-					0	-
Baseline_Pre		-0.07	0.02	-0.17	<0.01	-0.17	0.01	-0.25	<0.01	-0.25	<0.01	-0.38	<0.01	-	-

Diff HR=Post_HR - Pre_HR; Diff SpO2=Post SpO_2 – Pre SpO2; Diff RR = Post RR – Pre RR; Diff MAP = Post_MAP – Post_MAP;
Diff_VAS-A = Post_VAS-A – Pre_VAS-A; Diff_VAS-D = Post_ VAS-D – Pre_ VAS-D.
HR=Heart Rate; SpO2=Peripheral Capillary Oxygen Saturation; RR=respiratory rate; MAP=mean artery pressure; VAS-A = visual analog scale for anxiety; VAS-D = visual analog scale for dyspnea; Daily weaning duration=daily average time off ventilator measured in hours.

Table 6: Mixed-effect Model for All Outcome Measures (n=28)

		Diff_HR		Diff_SpO2		Diff_RR		Diff_MAP		Diff_VAS-A		Diff_VAS-D		Dailyweaningduration	
		Estimate	P	Estimate	P	Estimate	P	Estimate	P	Estimate	P	Estimate	P	Estimate	P
Treatment	Music	-2.03	**<0.01**	0.1	0.64	-2.86	**<0.01**	-0.3	0.71	-5.9225	**<0.01**	-6.6	**<0.01**	1.11	**0.03**
	Nomusic	0	-	0	-	0	-	0	-	0	-	0	-	0	-
Order	1	0.72	0.47	-0.12	0.68	-1.77	0.03	-0.23	-0.78	-3.4013	0.14	-2.48	0.47	-0.69	0.75
	2	0	-	0	-	0	-	0	-	0	-	0	-	0	-
Overall p-value for date		-	0.88	-	0.59	-	0.17	-	0.13	-	0.2	-	0.25	-	<0.01
Date	1	0.11	0.93	0.14	0.7	-0.18	0.86	2.48	0.09	-7.75	0.04	1.82	0.63	-4.78	<0.01
	2	0.13	0.91	-0.36	0.34	2.16	0.04	0.22	0.88	-4.97	0.19	4.69	0.2	-2	0.03
	3	0.3	0.81	0.13	0.73	1.2	0.24	1.19	0.41	-5.91	0.12	3.05	0.41	-1	0.28
	4	-0.07	0.96	-0.29	0.45	1.64	0.11	0.5	0.73	-9.59	0.01	-2.48	0.5	-1.2	0.19
	5	1.31	0.3	-0.23	0.55	0.92	0.38	3.33	0.03	-7.01	0.07	-2.23	0.55	-0.85	0.35
	6	0	-	0	-	0	-	0	-					0	-
Baseline_Pre		-0.06	0.03	-0.19	<0.01	-0.2	<0.01	-0.27	<0.01	-0.25	<0.01	-0.38	<0.01	-	-

Diff HR=Post_HR - Pre_HR; Diff SpO2=Post SpO2 – Pre SpO2; Diff RR = Post RR – Pre RR; Diff MAP = Post_MAP – Post_MAP; Diff_VAS-A = Post_VAS-A - Pre_VAS-A; Diff_VAS-D = Post_ VAS-D - Pre_ VAS-D.

HR=Heart Rate; SpO2=Peripheral Capillary Oxygen Saturation; RR=respiratory rate; MAP=mean artery pressure; VAS-A = visual analog scale for anxiety; VAS-D = visual analog scale for dyspnea; Daily weaning duration=daily average time off ventilator measured in hours.

BIBLIOGRAPHY

Almerud, S. (2003). Music therapy—a complementary treatment for mechanically ventilated intensive care patients. *Intensive and Critical Care Nursing, 19*(1), 21-30. doi: 10.1016/s0964-3397(02)00118-0

Arroliga, A., Frutos-Vivar, F., Hall, J., Esteban, A., Apezteguia, C., Soto, L., . . . International Mechanical Ventilation Study, G. (2005). Use of sedatives and neuromuscular blockers in a cohort of patients receiving mechanical ventilation. *Chest, 128*(2), 496-506. doi: 10.1378/chest.128.2.496

Arroliga, A. C., Thompson, B. T., Ancukiewicz, M., Gonzales, J. P., Guntupalli, K. K., Park, P. K., . . . Acute Respiratory Distress Syndrome, N. (2008). Use of sedatives, opioids, and neuromuscular blocking agents in patients with acute lung injury and acute respiratory distress syndrome. *Critical care medicine, 36*(4), 1083-1088. doi: 10.1097/CCM.0B013E3181653895

Balas, M. C., Burke, W. J., Gannon, D., Cohen, M. Z., Colburn, L., Bevil, C., . . . Vasilevskis, E. E. (2013). Implementing the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle into everyday care: opportunities, challenges, and lessons learned for implementing the ICU Pain, Agitation, and Delirium Guidelines. *Critical care medicine, 41*(9 Suppl 1), S116-127. doi: 10.1097/CCM.0b013e3182a17064

Baldwin, M. R., Narain, W. R., Wunsch, H., Schluger, N. W., Cooke, J. T., Maurer, M. S., . . . Bach, P. B. (2013). A prognostic model for 6-month mortality in elderly survivors of critical illness. *Chest, 143*(4), 910-919. doi: 10.1378/chest.12-1668

Barr, J., & Pandharipande, P. P. (2013). The pain, agitation, and delirium care bundle: synergistic benefits of implementing the 2013 Pain, Agitation, and Delirium Guidelines in an integrated and interdisciplinary fashion. *Critical care medicine, 41*(9 Suppl 1), S99-115. doi: 10.1097/CCM.0b013e3182a16ff0

Beaulieu-Boire, G., Bourque, S., Chagnon, F., Chouinard, L., Gallo-Payet, N., & Lesur, O. (2013). Music and biological stress dampening in mechanically-ventilated patients at the intensive care unit ward-a prospective interventional randomized crossover trial. *Journal of critical care, 28*(4), 442-450. doi: 10.1016/j.jcrc.2013.01.007

Blackwood, B., Alderdice, F., Burns, K., Cardwell, C., Lavery, G., & O'Halloran, P. (2011). Use of weaning protocols for reducing duration of mechanical ventilation in critically ill adult patients: Cochrane systematic review and meta-analysis. *BMJ, 342*, c7237. doi: 10.1136/bmj.c7237

Bradt, J., & Dileo, C. (2014). Music interventions for mechanically ventilated patients. *Cochrane Database Syst Rev, 12*, CD006902. doi: 10.1002/14651858.CD006902.pub3

Bradt, J., Potvin, N., Kesslick, A., Shim, M., Radl, D., Schriver, E., . . . Komarnicky-Kocher, L. T. (2015). The impact of music therapy versus music medicine on psychological outcomes and pain in cancer patients: a mixed methods study. *Support Care Cancer, 23*(5), 1261-1271. doi: 10.1007/s00520-014-2478-7

Campbell, G. B., & Happ, M. B. (2010). Symptom identification in the chronically critically ill. *AACN Adv Crit Care, 21*(1), 64-79. doi: 10.1097/NCI.0b013e3181c932a8

Carson, S. S., Kahn, J. M., Hough, C. L., Seeley, E. J., White, D. B., Douglas, I. S., . . . ProVent, I. (2012). A multicenter mortality prediction model for patients receiving prolonged mechanical ventilation. *Critical care medicine, 40*(4), 1171-1176. doi: 10.1097/CCM.0b013e3182387d43

Chan, M. F., Chung, Y. F., Chung, S. W., & Lee, O. K. (2009). Investigating the physiological responses of patients listening to music in the intensive care unit. *Journal of clinical nursing, 18*(9), 1250-1257. doi: 10.1111/j.1365-2702.2008.02491.x

Chlan, L., & Halm, M. A. (2013). Does music ease pain and anxiety in the critically ill? *Am J Crit Care, 22*(6), 528-532. doi: 10.4037/ajcc2013998

Chlan, L., & Heiderscheit, A. (2009). A Tool for Music Preference Assessment in Critically Ill Patients Receiving Mechanical Ventilatory Support. *Music Ther Perspect, 27*(1), 42-47. doi: 10.1093/mtp/27.1.42

Chlan, L. L. (1995). Psychophysiologic responses of mechanically ventilated patients to music: a pilot study. *Am J Crit Care, 4*(3), 233-238.

Chlan, L. L. (1998). Effectiveness of a music therapy intervention on relaxation and anxiety for patients receiving ventilatory assistance. *Heart & lung : the journal of critical care, 27*(3), 169-176.

Chlan, L. L. (2004). Relationship between two anxiety instruments in patients receiving mechanical ventilatory support. *J Adv Nurs, 48*(5), 493-499. doi: 10.1111/j.1365-2648.2004.03231.x

Chlan, L. L. (2009). A review of the evidence for music intervention to manage anxiety in critically ill patients receiving mechanical ventilatory support. *Archives of psychiatric nursing, 23*(2), 177-179. doi: 10.1016/j.apnu.2008.12.005

Chlan, L. L. (2010). Music Intervention. In: Snyder M, Lindquist R, (Eds.). *Complementary/Alternative Therapies in Nursing(6th ed.)* (pp. 91-105). New York, NY: Springer Publishing Company

Chlan, L. L., Engeland, W. C., Anthony, A., & Guttormson, J. (2007). Influence of music on the stress response in patients receiving mechanical ventilatory support: a pilot study. *Am J Crit Care, 16*(2), 141-145.

Chlan, L. L., Weinert, C. R., Heiderscheit, A., Tracy, M. F., Skaar, D. J., Guttormson, J. L., & Savik, K. (2013). Effects of patient-directed music intervention on anxiety and sedative exposure in critically ill patients receiving mechanical ventilatory support: a randomized clinical trial. *JAMA : the journal of the American Medical Association, 309*(22), 2335-2344. doi: 10.1001/jama.2013.5670

Conrad, C., Niess, H., Jauch, K. W., Bruns, C. J., Hartl, W., & Welker, L. (2007). Overture for growth hormone: requiem for interleukin-6? *Critical care medicine, 35*(12), 2709-2713.

Cox, C. E., Carson, S. S., Lindquist, J. H., Olsen, M. K., Govert, J. A., Chelluri, L., & Quality of Life After Mechanical Ventilation in the Aged, I. (2007). Differences in one-year health outcomes and resource utilization by definition of prolonged mechanical ventilation: a prospective cohort study. *Crit Care, 11*(1), R9. doi: 10.1186/cc5667

Cox, C. E., Martinu, T., Sathy, S. J., Clay, A. S., Chia, J., Gray, A. L., . . . Tulsky, J. A. (2009). Expectations and outcomes of prolonged mechanical ventilation. *Critical care medicine, 37*(11), 2888-2894; quiz 2904. doi: 10.1097/CCM.0b013e3181ab86ed

Davis, W. B. (2003). Ira Maximilian Altshuler: psychiatrist and pioneer music therapist. *J Music Ther, 40*(3), 247-263.

Dermot Frengley, J., Sansone, G. R., Shakya, K., & Kaner, R. J. (2014). Prolonged mechanical ventilation in 540 seriously ill older adults: effects of increasing age on clinical outcomes and survival. *Journal of the American Geriatrics Society, 62*(1), 1-9. doi: 10.1111/jgs.12597

Egerod, I., Christensen, B. V., & Johansen, L. (2006). Trends in sedation practices in Danish intensive care units in 2003: a national survey. *Intensive Care Med, 32*(1), 60-66. doi: 10.1007/s00134-005-2856-1

Ely, E. W., Meade, M. O., Haponik, E. F., Kollef, M. H., Cook, D. J., Guyatt, G. H., & Stoller, J. K. (2001). Mechanical ventilator weaning protocols driven by nonphysician health-care professionals: evidence-based clinical practice guidelines. *Chest, 120*(6 Suppl), 454S-463S.

Guttormson, J. L., Chlan, L., Weinert, C., & Savik, K. (2010). Factors influencing nurse sedation practices with mechanically ventilated patients: a U.S. national survey. *Intensive Crit Care Nurs, 26*(1), 44-50. doi: 10.1016/j.iccn.2009.10.004

Han, L., Li, J. P., Sit, J. W., Chung, L., Jiao, Z. Y., & Ma, W. G. (2010). Effects of music intervention on physiological stress response and anxiety level of mechanically ventilated patients in China: a randomised controlled trial. *Journal of clinical nursing, 19*(7-8), 978-987. doi: 10.1111/j.1365-2702.2009.02845.x

Happ, M. B., Baumann, B. M., Sawicki, J., Tate, J. A., George, E. L., & Barnato, A. E. (2010). SPEACS-2: intensive care unit "communication rounds" with speech language pathology. *Geriatric nursing, 31*(3), 170-177. doi: 10.1016/j.gerinurse.2010.03.004

Happ, M. B., Garrett, K., Thomas, D. D., Tate, J., George, E., Houze, M., . . . Sereika, S. (2011). Nurse-patient communication interactions in the intensive care unit. *Am J Crit Care, 20*(2), e28-40. doi: 10.4037/ajcc2011433

Heiderscheit, A., Breckenridge, S. J., Chlan, L. L., & Savik, K. (2014). Music preferences of mechanically ventilated patients participating in a randomized controlled trial. *Music and medicine, 6*(2), 29-38.

Hermans, G., Van Mechelen, H., Clerckx, B., Vanhullebusch, T., Mesotten, D., Wilmer, A., . . . Van den Berghe, G. (2014). Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. *Am J Respir Crit Care Med, 190*(4), 410-420. doi: 10.1164/rccm.201312-2257OC

Herridge, M. S., Tansey, C. M., Matte, A., Tomlinson, G., Diaz-Granados, N., Cooper, A., . . . Canadian Critical Care Trials, G. (2011). Functional disability 5 years after acute respiratory distress syndrome. *The New England journal of medicine, 364*(14), 1293-1304. doi: 10.1056/NEJMoa1011802

Hofso, K., & Coyer, F. M. (2007a). Part 1. Chemical and physical restraints in the management of mechanically ventilated patients in the ICU: contributing factors. *Intensive Crit Care Nurs, 23*(5), 249-255. doi: 10.1016/j.iccn.2007.04.003

Hofso, K., & Coyer, F. M. (2007b). Part 2. Chemical and physical restraints in the management of mechanically ventilated patients in the ICU: a patient perspective. *Intensive Crit Care Nurs, 23*(6), 316-322. doi: 10.1016/j.iccn.2007.04.002

Hunter, B. C., Oliva, R., Sahler, O. J., Gaisser, D., Salipante, D. M., & Arezina, C. H. (2010). Music therapy as an adjunctive treatment in the management of stress for patients being weaned from mechanical ventilation. *J Music Ther, 47*(3), 198-219.

Jackson, D. L., Proudfoot, C. W., Cann, K. F., & Walsh, T. (2010). A systematic review of the impact of sedation practice in the ICU on resource use, costs and patient safety. *Crit Care, 14*(2), R59. doi: 10.1186/cc8956

Jubran, A., Grant, B. J., Duffner, L. A., Collins, E. G., Lanuza, D. M., Hoffman, L. A., & Tobin, M. J. (2013). Effect of pressure support vs unassisted breathing through a tracheostomy collar on weaning duration in patients requiring prolonged mechanical ventilation: a randomized trial. *JAMA : the journal of the American Medical Association, 309*(7), 671-677. doi: 10.1001/jama.2013.159

Jubran, A., Lawm, G., Kelly, J., Duffner, L. A., Gungor, G., Collins, E. G., . . . Tobin, M. J. (2010). Depressive disorders during weaning from prolonged mechanical ventilation. *Intensive Care Med, 36*(5), 828-835. doi: 10.1007/s00134-010-1842-4

Kahn, J. M., Benson, N. M., Appleby, D., Carson, S. S., & Iwashyna, T. J. (2010). Long-term acute care hospital utilization after critical illness. *JAMA : the journal of the American Medical Association, 303*(22), 2253-2259. doi: 10.1001/jama.2010.761

Kahn, J. M., Werner, R. M., David, G., Ten Have, T. R., Benson, N. M., & Asch, D. A. (2013). Effectiveness of long-term acute care hospitalization in elderly patients with chronic critical illness. *Med Care, 51*(1), 4-10. doi: 10.1097/MLR.0b013e31826528a7

Kim, Y. S., Kleerup, E. C., Ganz, P. A., Ponce, N. A., Lorenz, K. A., & Needleman, J. (2015). Medicare Payment Policy Creates Incentives For Long-Term Care Hospitals To Time Discharges For Maximum Reimbursement. *Health Aff (Millwood), 34*(6), 907-915. doi: 10.1377/hlthaff.2014.0778

Knebel, A. R., Janson-Bjerklie, S. L., Malley, J. D., Wilson, A. G., & Marini, J. J. (1994). Comparison of breathing comfort during weaning with two ventilatory modes. *Am J Respir Crit Care Med, 149*(1), 14-18. doi: 10.1164/ajrccm.149.1.8111572

Koelsch, S., Fritz, T., Schulze, K., Alsop, D., & Schlaug, G. (2005). Adults and children processing music: an fMRI study. *Neuroimage, 25*(4), 1068-1076. doi: 10.1016/j.neuroimage.2004.12.050

Kollef, M. H., Levy, N. T., Ahrens, T. S., Schaiff, R., Prentice, D., & Sherman, G. (1998). The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest, 114*(2), 541-548.

Korhan, E. A., Khorshid, L., & Uyar, M. (2011). The effect of music therapy on physiological signs of anxiety in patients receiving mechanical ventilatory support. *Journal of clinical nursing, 20*(7-8), 1026-1034. doi: 10.1111/j.1365-2702.2010.03434.x

Kress, J. P., Pohlman, A. S., O'Connor, M. F., & Hall, J. B. (2000). Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *The New England journal of medicine, 342*(20), 1471-1477. doi: 10.1056/NEJM200005183422002

Lee, O. K., Chung, Y. F., Chan, M. F., & Chan, W. M. (2005). Music and its effect on the physiological responses and anxiety levels of patients receiving mechanical ventilation: a pilot study. *Journal of clinical nursing, 14*(5), 609-620. doi: 10.1111/j.1365-2702.2004.01103.x

Leroy, G., Devos, P., Lambiotte, F., Thevenin, D., & Leroy, O. (2014). One-year mortality in patients requiring prolonged mechanical ventilation: multicenter evaluation of the ProVent score. *Crit Care, 18*(4), R155. doi: 10.1186/cc13994

Maranto, C. (1993). Applications of music in medicine. In M. Heal & T. Wigram (Eds.) *Music Therapy in health and education* (pp. 153-174). London: J. Kingsley.

McCartney, J. R., & Boland, R. J. (1994). Anxiety and delirium in the intensive care unit. *Crit Care Clin, 10*(4), 673-680.

McKinley, S., Stein-Parbury, J., Chehelnabi, A., & Lovas, J. (2004). Assessment of anxiety in intensive care patients by using the Faces Anxiety Scale. *Am J Crit Care., 13*(2), 146-152.

McNicoll, L., Pisani, M. A., Ely, E. W., Gifford, D., & Inouye, S. K. (2005). Detection of delirium in the intensive care unit: comparison of confusion assessment method for the intensive care unit with confusion assessment method ratings. *Journal of the American Geriatrics Society, 53*(3), 495-500. doi: 10.1111/j.1532-5415.2005.53171.x

Meade, M., Guyatt, G., Griffith, L., Booker, L., Randall, J., & Cook, D. J. (2001). Introduction to a series of systematic reviews of weaning from mechanical ventilation. *Chest, 120*(6 Suppl), 396S-399S.

Mehta, S., Burry, L., Cook, D., Fergusson, D., Steinberg, M., Granton, J., . . . Canadian Critical Care Trials, G. (2012). Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. *JAMA : the journal of the American Medical Association, 308*(19), 1985-1992.

Menon, V., & Levitin, D. J. (2005). The rewards of music listening: response and physiological connectivity of the mesolimbic system. *Neuroimage, 28*(1), 175-184. doi: 10.1016/j.neuroimage.2005.05.053

Munro, S., & Mount, B. (1978). Music therapy in palliative care. *Can Med Assoc J, 119*(9), 1029-1034.

Nelson, J. E., Meier, D. E., Litke, A., Natale, D. A., Siegel, R. E., & Morrison, R. S. (2004). The symptom burden of chronic critical illness. *Critical care medicine, 32*(7), 1527-1534.

Nelson, J. E., Meier, D. E., Oei, E. J., Nierman, D. M., Senzel, R. S., Manfredi, P. L., . . . Morrison, R. S. (2001). Self-reported symptom experience of critically ill cancer patients receiving intensive care. *Critical care medicine, 29*(2), 277-282.

Nichols, W., & O'Rourke, M. (1988). *McDonald's blood flow in arteries: theoretical, experimental and clinical principles, 4th ed.* London: Edward Arnold.

Nilsen, M. L., Sereika, S., & Happ, M. B. (2013). Nurse and patient characteristics associated with duration of nurse talk during patient encounters in ICU. *Heart & lung : the journal of critical care, 42*(1), 5-12. doi: 10.1016/j.hrtlng.2012.10.003

Phipps, M. A., Carroll, D. L., & Tsiantoulas, A. (2010). Music as a therapeutic intervention on an inpatient neuroscience unit. *Complementary therapies in clinical practice, 16*(3), 138-142. doi: 10.1016/j.ctcp.2009.12.001

Puntillo, K. A., Smith, D., Arai, S., & Stotts, N. (2008). Critical care nurses provide their perspectives of patients' symptoms in intensive care units. *Heart & lung : the journal of critical care, 37*(6), 466-475. doi: 10.1016/j.hrtlng.2008.02.002

Rattray, J., Johnston, M., & Wildsmith, J. A. (2004). The intensive care experience: development of the ICE questionnaire. *J Adv Nurs, 47*(1), 64-73. doi: 10.1111/j.1365-2648.2004.03066.x

Rotondi, A. J., Chelluri, L., Sirio, C., Mendelsohn, A., Schulz, R., Belle, S., . . . Pinsky, M. R. (2002). Patients' recollections of stressful experiences while receiving prolonged mechanical ventilation in an intensive care unit. *Critical care medicine, 30*(4), 746-752.

SAS Institute. (2015). The SAS system for Windows. Release 9.4. SAS Inst. (Version 9.4). Cary, NC.

Scheinhorn, D. J., Hassenpflug, M. S., Votto, J. J., Chao, D. C., Epstein, S. K., Doig, G. S., . . . Petrak, R. A. (2007). Post-ICU mechanical ventilation at 23 long-term care hospitals: a multicenter outcomes study. *Chest, 131*(1), 85-93. doi: 10.1378/chest.06-1081

Seneff, M. G., Wagner, D., Thompson, D., Honeycutt, C., & Silver, M. R. (2000). The impact of long-term acute-care facilities on the outcome and cost of care for patients undergoing prolonged mechanical ventilation. *Critical care medicine, 28*(2), 342-350.

Sessler, C. N., Gosnell, M. S., Grap, M. J., Brophy, G. M., O'Neal, P. V., Keane, K. A., . . . Elswick, R. K. (2002). The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med, 166*(10), 1338-1344. doi: 10.1164/rccm.2107138

Sessler, C. N., & Varney, K. (2008). Patient-focused sedation and analgesia in the ICU. *Chest, 133*(2), 552-565. doi: 10.1378/chest.07-2026

Sneyers, B., Laterre, P. F., Bricq, E., Perreault, M. M., Wouters, D., & Spinewine, A. (2013). What stops us from following sedation recommendations in intensive care units? A multicentric qualitative study. *Journal of critical care*. doi: 10.1016/j.jcrc.2013.11.004

Tang, H. Y., & Vezeau, T. (2010). The use of music intervention in healthcare research: a narrative review of the literature. *The journal of nursing research : JNR, 18*(3), 174-190. doi: 10.1097/JNR.0b013e3181efe1b1

Tanios, M. A., de Wit, M., Epstein, S. K., & Devlin, J. W. (2009). Perceived barriers to the use of sedation protocols and daily sedation interruption: a multidisciplinary survey. *Journal of critical care, 24*(1), 66-73. doi: 10.1016/j.jcrc.2008.03.037

Tate, J., & Happ, M. B. (2012). The Confusion Assessment Method for the ICU (CAM-ICU). *Best Practices in Nursing Care to Older Aldults*(25).

Tate, J. A., Devito Dabbs, A., Hoffman, L. A., Milbrandt, E., & Happ, M. B. (2012). Anxiety and agitation in mechanically ventilated patients. *Qual Health Res, 22*(2), 157-173. doi: 10.1177/1049732311421616

Tate, J. A., Sereika, S., Divirgilio, D., Nilsen, M., Demerci, J., Campbell, G., & Happ, M. B. (2013). Symptom communication during critical illness: the impact of age, delirium, and delirium presentation. *J Gerontol Nurs, 39*(8), 28-38. doi: 10.3928/00989134-20130530-03

Thomas, L. A. (2003). Clinical management of stressors perceived by patients on mechanical ventilation. *AACN Clin Issues, 14*(1), 73-81.

Tracy, M. F., & Chlan, L. (2011). Nonpharmacological interventions to manage common symptoms in patients receiving mechanical ventilation. *Critical care nurse, 31*(3), 19-28. doi: 10.4037/ccn2011653

White, A. C., O'Connor, H. H., & Kirby, K. (2008). Prolonged mechanical ventilation: review of care settings and an update on professional reimbursement. *Chest, 133*(2), 539-545. doi: 10.1378/chest.07-0656

Wong, H. L., Lopez-Nahas, V., & Molassiotis, A. (2001). Effects of music therapy on anxiety in ventilator-dependent patients. *Heart & lung : the journal of critical care, 30*(5), 376-387. doi: 10.1067/mhl.2001.118302

Zilberberg, M. D., de Wit, M., Pirone, J. R., & Shorr, A. F. (2008). Growth in adult prolonged acute mechanical ventilation: implications for healthcare delivery. *Critical care medicine, 36*(5), 1451-1455. doi: 10.1097/CCM.0b013e3181691a49

Zilberberg, M. D., de Wit, M., & Shorr, A. F. (2012). Accuracy of previous estimates for adult prolonged acute mechanical ventilation volume in 2020: update using 2000-2008 data. *Critical care medicine, 40*(1), 18-20. doi: 10.1097/CCM.0b013e31822e9ffd

Zilberberg, M. D., Luippold, R. S., Sulsky, S., & Shorr, A. F. (2008). Prolonged acute mechanical ventilation, hospital resource utilization, and mortality in the United States. *Critical care medicine, 36*(3), 724-730. doi: 10.1097/CCM.0B013E31816536F7